

Atty Dkt. No.: UCAL-161DIV
USSN: 09/922,483
Exhibit 1

EXPRESS MAIL NO. EV462737349US		
DECLARATION OF ROSS STEIN UNDER 37 C.F.R. § 1.132 Address to: Commissioner for Patents Alexandria, VA 22313-1450	Attorney Docket Confirmation No.	UCAL161DIV 7273
	First Named Inventor	Steven Finkbeiner
	Application Number	09/922,483
	Filing Date	August 2, 2001
	Group Art Unit	1648
	Examiner Name	U. Winkler
	Title	<i>Antibodies specific for proteins having polyglutamine expansions</i>

Dear Sir:

1. I, Ross Stein declare and say I am an expert in the field of enzyme kinetics and drug discovery. I currently am affiliated with the Brigham and Women's Hospital in the Department of Neurology, the Laboratory for Drug Discovery in Neurodegeneration (LDDN). A copy of my curriculum vitae is provided herewith as Exhibit 2.

2. I understand that certain of the currently pending claims in the above-captioned patent application recite a screening method that assays the ability of a test agent to inhibit binding between an antibody specific for a polyglutamine expansion and a protein containing such a polyglutamine expansion. The screening method identifies agents that modulate the binding interaction between a protein comprising a polyglutamine expansion and a cellular target of such a protein.

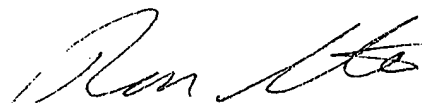
3. I understand that a United States Patent and Trademark Office Examiner has rejected such claims on the basis that measuring the interaction between a polyglutamine expansion-containing protein and an antibody specific for a polyglutamine expansion will not provide any insight into the interaction of the polyglutamine expansion-containing protein and its cellular target.

4. In my opinion, it is reasonable to use such an assay to identify agents that inhibit binding of a protein containing a polyglutamine expansion to its cellular target. The antibody that will be used in this assay has a specific binding site for a toxic conformation of polyglutamine. It is not unreasonable to assume that the binding site on the antibody might have structural features and binding properties for polyglutamine that are similar to binding sites on the cellular proteins that mediate the toxic effects of polyglutamine. Therefore, small drug-like molecules that bind to the site on the antibody, thereby blocking polyglutamine from binding to the antibody, might also bind to these cellular proteins. I believe that this type of assay represents an important and valuable approach to identifying new therapeutic agents for neurodegenerative disorders.

5. I am principle investigator on a grant application submitted to the National Institute of Neurological Disorders and Stroke (NINDS) that includes a collaboration with Dr. Steven Finkbeiner and the use of as this assay as a key component. The grant application included the proposed use of such an assay in a high throughput screen format to identify agents that inhibit binding of a protein containing a polyglutamine expansion to its cellular target. This grant was reviewed be an NINDS Special Emphasis panel on April 23, 2004. The comments of the panel were strongly supportive of the science of the grant, including this assay.

6. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title XVIII of the United States Code, and that such will false statements may jeopardize the validity of the application or any patent issuing thereon.

7/17/04
Date



Ross Stein



U.S. Patent Application No. 09/922,483
Exhibit 2

PART I: General Information

Date Prepared: 03/10/2004

Name: Ross Lee Stein, Ph.D.

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Place of Birth: St. Louis, MO

Education

Year	Degree	Institution
1974	B.S., Chemistry	Southern Illinois University Edwardsville, IL
1978	Ph.D., Biochemistry	Indiana University Bloomington, IN

Postdoctoral Training

Year	Title	Place of Training	Specialty/Discipline
1978 - 1979	Postdoctoral Fellow	Washington University School of Medicine St. Louis, MO	Enzymology/Pharmacology
1979 - 1981	Research Associate	University of Kansas Lawrence, KS	Mechanistic Enzymology

Professional Positions

<u>Year</u>	<u>Position/Title</u>	<u>Institution</u>
1981 – 1984	Research Biochemist Pharmacology Department	Stuart Pharmaceuticals Wilmington, DE
1984 – 1987	Senior Research Biochemist Pharmacology Department	Stuart Pharmaceuticals Wilmington, DE
1987 - 1989	Associate Director Department of Enzymology	Merck Research Labs Rahway, NJ
1989 - 1992	Director Department of Enzymology	Merck Research Labs Rahway, NJ
1992 - 1993	Director Enzymology	Genesis Pharmaceuticals Cambridge, MA
1993 - 1995	Executive Director Biochemistry	ProScript, Inc. Cambridge, MA
1995 - 1998	Vice President Biochemistry	ProScript, Inc. Cambridge, MA
1998	Senior Director Biochemistry	Cubist Pharmaceuticals Cambridge, MA
1999 – 2001	Research Fellow Chemical Enzymology	DuPont Pharmaceuticals Wilmington, DE
2001 - present	Director Laboratory for Drug Discovery in Neurodegeneration	Harvard Medical School Boston, MA
2003 - present	Associate Professor Department of Neurology	Harvard Medical School Boston, MA

Professional Societies

<u>Year</u>	<u>Society</u>	<u>Role</u>
1972 - present	American Chemical Society	Member
1976 - present	FASEB	Member
1981 - present	AAAS	Member

PART II: Research, Teaching, and Clinical Contributions

Summary of Research and Managerial Contributions

My research contributions have been in the areas of mechanistic enzymology and drug discovery. I have contributed to the understanding of mechanisms of catalysis of several enzymes, including: purine nucleoside phosphorylase, elastase, stromelysin, peptidyl prolyl *cis-trans* isomerase, the proteasome, ubiquitin C-terminal hydrolase, signal peptidase, γ -glutamyl transpeptidase, penicillin binding proteins, and aryl acylamidase. In all cases, I have applied precise kinetics-based probes to elucidate key structural features of catalytic transition states. The knowledge gained from these studies has been applied to the design and mechanistic characterization of inhibitors of these enzymes and, in several cases, to the development of new therapeutics for human disease. For elastase and the proteasome, these basic mechanistic studies contributed in a direct way to the development of a drug that was in clinical trials in the early 1990's for cystic fibrosis (i.e., elastase inhibitor) and a drug, VELCADETM, that has been approved by the FDA for the treatment of certain cancers (i.e., proteasome inhibitor).

As a manager, I have built and run research departments in both pharmaceutical and biotech companies. At Merck, I built the Department of Enzymology from seven scientists to about twenty five. This department contributed broadly to many projects at Merck that had enzymes as their therapeutic targets. Several of these projects resulted in drugs that went into human clinical trials. At ProScript, I was the company's first scientist and helped build the research department to about thirty scientists. As head of Biochemistry, I managed a staff that worked on the development of assays and elucidation of mechanism for enzymes of the ubiquitin-proteasome pathway. These enzymes include the proteasome, ubiquitin activating enzyme, ubiquitin conjugating enzymes, and ubiquitin C-terminal hydrolases. The work of this group of scientists was instrumental in the development of a proteasome inhibitor that is now in clinical trials.

Current Research and Managerial Activities

My current activities as Director of the Laboratory for Drug Discovery in Neurodegeneration include hiring staff, managing the day-to-day operation of the facility, working with HMS staff and post-doctoral fellows to develop and optimize assays to be run as high-throughput screens, fund-raising activities, and conducting mechanistic studies on the compounds that are discovered in the various screens.

My research interests are in the areas of enzyme catalysis and inhibition. I am concerned with trying to understand the mechanistic origins of the enormous rate-accelerations that are effected by enzymes and how knowledge gained about enzymatic catalysis can be used to design inhibitors and understand how enzyme inhibitors work. Specific to these interests, I am currently undertaken two projects: acylation chemistry and dynamics of serine hydrolases and mechanisms of transglutaminase-catalyzed transamidation.

Research Funding

“Harvard Center for Neurodegeneration and Repair Core D”

01/01/01 – 12/31/05

Principal Investigator: Peter T. Lansbury, Jr., Ph.D.

Agency: Harvard Medical School

The goals of Core D of the Harvard Center for Neurodegeneration and Repair are to discover new drugs for the treatment of neurodegenerative diseases and to discover tool-compounds that can be used to probe pathogenesis in cell- and animal-models of disease. This project is being done in the Laboratory for Drug Discovery for Neurodegeneration, which was created as the means to best attain the overarching goals of Core D. The ongoing activities of the LDDN include the development and execution of novel cell-, enzyme-, and receptor-based assays for multiple disease targets. These assays are run against an in-house library of approximately 52,000 compounds. This project also includes medicinal chemistry-directed optimization of active compounds that are discovered during the screening process.

“Inhibition of antigen Presentation in Multiple Sclerosis”

12/1/02 – 11/30/06

Principal Investigator: Kai W. Wucherpfenning, M.D., Ph.D.

Agency: NIH

The specific aims of the project are: To develop robust assays for high-throughput screening of small molecules that block presentation of myelin peptides (Aim 1), to screen a large and diverse collection of small molecules under conditions relevant for intracellular peptide loading (Aim 2), and to study the mechanisms by which lead compounds inhibit presentation of myelin peptides (Aim 3). We are in a unique position to pursue this project, based on our combined expertise in immunology and drug discovery, and the preliminary data demonstrate that both assay development and high throughput screening are feasible.

“Chemical Genetics and Regulated Intramembrane Proteolysis”

7/1/03 – 6/30/08

Principal Investigator: Michael S. Wolfe, Ph.D.

Agency: NIH

The goal of this project is to apply the principles of chemical genetics to discover bio-organic agents suitable for the study of N and APP processing in signaling, developmental biology and human disease and to determine the protein targets of these agents.

“Metabolic Pathways and Defects in Fructose Metabolism”

7/1/03 – 6/30/08

Principal Investigator: Dean R. Tolan, Ph.D.

Agency: NIH

The major goals of this project are to 1) define sites for fructose assimilation and utilization using a combination of bioinformatics and molecular approaches, 2) determine a high-resolution structure of AP-aldolase, and use it to find stabilizing small-molecule ligands by both structure-based ligand design (SBLD) and using combinatorial chemistry, 3) create animal models for HFI using gene-targeting techniques, and 4) identify HFI mutations in the diverse US population, in particular Hispanic, African-American, and other ethnic groups that have not been well characterized, and correlate these findings to any specific phenotypes in these ethnic groups

“Compound Identification in Assays for Tau Pathology”

2/1/03 – 1/31/05

Principal Investigator: Kenneth S. Kosik, M.D.

Agency: NIH

Period: 2/1/03 – 1/31/05

The goal of this project is to develop two high through-put screens aimed at the discovery of compounds with a potential impact on neurodegenerative pathologies related to tau

Teaching Responsibilities

My teaching responsibilities include formal and informal lectures, and the mentoring of post-doctoral students and technicians in the areas of enzyme kinetics, enzyme mechanism, drug discovery, and high throughput screening. Among the lectures are formal presentations at the Center for Neurologic Diseases (CND), Brigham and Women’s Hospital and a lecture series on enzyme kinetics and mechanism given within the Laboratory for Drug Discovery in Neurodegeneration (LDDN). These lectures include the following:

“Role of Mechanistic Studies in Drug Discovery”, CND, June, 2001.

“Principles of High-Throughput Screening”, LDDN, September, 2001.

“Role of Mechanistic Studies in Drug Discovery – Assay Development”, LDDN, October, 2001.

“Role of Mechanistic Studies in Drug Discovery – Kinetic Analysis of Enzyme Inhibitors”, LDDN, December, 2001.

“Role of Mechanistic Studies in Drug Discovery – Principles of Elucidating Enzyme Mechanisms for Catalysis and Inhibition. I”, LDDN, February, 2002.

“Role of Mechanistic Studies in Drug Discovery – Principles of Elucidating Enzyme Mechanisms for Catalysis and Inhibition. II”, LDDN, May, 2002.

“Transglutaminase as a Target for Huntington’s Disease – Mechanism, Inhibitor Design, and High-Throughput Screening”, LDDN, February, 2003.

Mentoring has included numerous sessions with many post-docs, including:

Melissa Nicholson (Wucherpennig lab, DFCI) – kinetics of receptor binding

Craig Justman (Lansbury lab, BWH) – mechanism of synuclein aggregation

Jae Ahn (Kosik lab, BWH) – kinase kinetics and screening for inhibitors

Malcolm Leissring (Selkoe lab, BWH) – kinetics of protease action

Yichin Liu (Lansbury lab, BWH) – kinetics and mechanism of ubiquitin hydrolases

David Wilson (Stein lab, LDDN) – kinetics and mechanism of tau aggregation

April Case (Stein lab, LDDN) – kinetics and mechanism of transglutaminase

Teaching Experience – Invited Regional, National and International Contributions

1. "Catalysis by Human Leukocyte Elastase." Presented to the Department of Chemistry, University of Kansas, July 1982.
2. "Catalysis by Human Leukocyte Elastase." Presented to the Department of Chemistry, Southern Illinois University, December 1982.
3. "An Automated System for Enzyme Kinetics." Presented at the First International Symposium on Laboratory Robotics, October 1983.
4. "Catalysis by Human Leukocyte Elastase." Presented to the Department of Chemistry, Georgia Institute of Technology, January 1984.
5. "Role of Subsite Interactions in Catalysis by Human Leukocyte Elastase." Presented to the Department of Pharmacology, Institute for Medical Research, Louis Pasteur University, Strasbourg, France, October, 1984.
6. "Role of Subsite Interactions in Catalysis by Human Leukocyte Elastase." Presented to the Department of Chemistry, Southern Illinois University, October, 1984.
7. "Mechanism of Action of Human Leukocyte Elastase." N.I.H. Workshop on Elastase Inhibition, June 10-11, 1985.
8. "Mechanism of Action of Human Leukocyte Elastase." Presented to the Department of Chemistry, University of Kansas, October 1985.
9. "Mechanism of Action of Human Leukocyte Elastase." Presented to the Department of Chemistry, Wichita State University, October 1985.
10. "The Proton Inventory as a Probe of Protease Mechanism." Gordon Research Conference on Isotopes, February 1986.
11. "Mechanisms of Slow-Binding Inhibition of Serine Proteases." Presented to the Department of Chemistry, University of Kansas, November 1987.
12. "Mechanistic Insights into the Substrate Specificity of Human Leukocyte Elastase." Presented to the Department of Chemistry, University of Kansas (1987).
13. "Mechanisms of Slow-Binding Inhibition of Serine Proteases." Midwest American Chemical Society Meeting, Wichita State University, November 1987.
14. "Mechanisms of Slow-Binding Inhibition of Serine Proteases." Presented to the Department of Biochemistry, Tufts University, December 1987.

15. "Mechanisms of Slow-Binding Inhibition of Serine Proteases." Presented to the Department of Chemistry, University of Iowa, April 1988.
16. "Mechanistic Studies of Metalloproteases." Presented to the Department of Chemistry, Texas A&M University, March 1989.
17. "Mechanistic Studies of Metalloproteases." Presented to the Department of Biochemistry, University of Washington, April 1989.
18. "Mechanistic Studies of Peptidyl Prolyl cis-trans Isomerase." Presented to the Department of Chemistry, Florida State University, April 1990.
19. "Mechanistic Studies of Peptidyl Prolyl cis-trans Isomerase." Presented to the Medical School, Louis Pasteur University, Strasbourg, France, October 1990.
20. "Studies of the Matrix Metalloproteinase, Stromelysin." Presented to the Dept. of Pharmacy, Louis Pasteur University, Strasbourg, France, October 1990.
21. "The Proton Inventory as a Probe of Enzyme Mechanism." Presented to the Dept. of Pharmacy, Louis Pasteur University, Strasbourg, France, October 1990.
22. "Mechanistic Studies of Peptidyl Prolyl cis-trans Isomerase." Presented at Cyclosporin, Immunosuppression and Protein Folding, an international meeting held in Brandenburg, Germany, October 1990.
23. "Mechanistic Studies of Peptidyl Prolyl cis-trans Isomerase." Department of Biophysics, Boston University Medical School, November 1990.
24. "Mechanistic Studies of Peptidyl Prolyl cis-trans Isomerase." Department of Chemistry, Wesleyan University, September 1990.
25. "Mechanistic Studies of Stromelysin Catalysis and Inhibition." International Conference on Cartilage Destruction and Repair, Redbank, NJ, September 1991.
26. "Solvent and Secondary Kinetic Isotope Effects as Probes of Protease Catalysis and Inhibition." Gordon Conference on Isotope Effects in the Physical and Life Sciences, Ventura, CA, March 1992.
27. "Mechanistic Studies of Metalloproteinase Catalysis and Inhibition" Gordon Conference on Proteolytic Enzymes, Plymouth, N.H., June 1992
28. "Mechanistic Studies of Peptidyl Prolyl cis-trans Isomerase." Symposium on Enzymes, Inhibitors and Drug Design", Antwerp, Belgium, November 1992.

29. "Inhibition of Proteasome-Dependent Activation of NF- κ B: A Novel Strategy for the Development of Anti-Inflammatory Agents", SRI Symposium: On the Cutting Edge of Anti-Inflammatory Drug Discovery", February 1996.
30. "Novel Inhibitors of the Proteasome", Gordon Conference on Proteolytic Enzymes, Plymouth, N.H., July 1996.
31. "Inhibition of Proteasome-Dependent Activation of NF- κ B: A Novel Strategy for the Development of Anti-Inflammatory Agents", IBC's 2nd International Conference on Proteases Inhibitors, Washington, D.C. February 1997.
32. "Enzymology and Inhibition of the Ubiquitin-Proteasome Pathway", Gordon Research Conference on Enzymes, Coenzyme, and Metabolic Pathways, Kimball Union Academy, N.H., July, 1998.
33. "Kinetic and Mechanistic Studies of Signal Peptidase – A New Target for the Development of Antibacterial Agents", Temple University, School, of Medicine, Department of Biochemistry, May, 2000.
34. "Drug Discovery for Neurodegenerative Diseases at Harvard Medical School", Meeting of the Parkinson Study Group, Santa Fe, NM, November, 2001.
35. "High-Throughput Screening and Drug Discovery for Neurodegenerative Diseases", Neurology Grand Rounds at Rhode Island Hospital, Brown University, School of Medicine, Department of Neurology, May, 2002.
36. "High-Throughput Screening and Drug Discovery for Neurodegenerative Diseases", Meeting of the Parkinson's Study Group, San Diego, CA, May, 2002.
37. "Ensemble of Transition States. Role of Conformational Mobility in Enzyme Catalysis", 29th Reaction Mechanisms Conference, Columbus, OH, June, 2002.
38. "New Models for Drug Discovery: Charting the Evolving Relationship between the Public and Private Sectors" Panel discussion at the IBC Drug Discovery Technology Conferency, Boston, MA, August, 2002.
39. "The Role of Mechanistic Studies in the Design of Enzyme Inhibitors," session organizer for national meeting of the American Chemical Society, Boston, MA, August, 2002.
40. "A New Model for Drug Discovery", Massachusetts Biotechnology Council's Conference on Biotechnology Investment, Boston, MA, October, 2002.
41. "A New Model for Drug Discovery", The Cure Parkinson's Project Conference – Accelerating the Cure, Chacago, IL, December, 2002.

42. "A New Model for Drug Discovery", Partners Program in Neurodegenerative Diseases 6th Annual Colluquim – Current Approaches to Understanding Neurodegenerative Diseases, Boston, MA, March 21, 2003.
43. "The Final Frontier – Therapies to Treat Neurological Disorders", session organizer, BIO 2003, Washington, DC, June 22-25, 2003.
44. "A New Model for Academic-Based Drug Discovery", BIO 2003, Washington, DC, June 22-25, 2003.
45. "Misguided Folding and Degradation of Protein – New Opportunities for Therapeutics in Neurodegenerative Diseases", BIO 2003, Washington, DC, June 22-25, 2003.
46. "A New Model for Academic-Based Drug Discovery", Drug Discovery Technology World Congress, Boston, MA, August 10-15, 2003.
47. "A New Model for Academic-Based Drug Discovery", Fourth Annual Institute for the Study of Agining Investiagotor's Meeting, Teaneck, NJ, October 1-3, 2003.

Part III: Bibliography

Original Articles

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2. Vogler EA, Stein RL and Hayes JM. Mechanism of formation of grignard reagents. J. Amer. Chem. Soc. 1978;100:3161-66.
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CLON-015	09/440,829	Transmittal, Fee Sheet <i>in duplicate</i> , IDS, SB08A, (5) Cited References	BEF	\$180
CRMD-006	10/792,657	Transmittal, Fee Sheet <i>in duplicate</i> , Copy of Notice to File Missing Parts, Supplemental ADS, Executed Declaration, Formal Drawing Transmittal, (14) Sheets of Figures	CML	\$603
UCAL-243	10/723,589	Transmittal, Fee Sheet <i>in duplicate</i> , Petition for a 3 Month Extension of Time, Supplemental ADS, Executed Declaration	KYB	\$2,338
RIGL-005CON	10/057,467	Transmittal, Fee Sheet <i>in duplicate</i> , Amendment After Final Rejection, (2) Terminal Disclaimers, SB08A	JSK	\$110
LBLB-002CIPCON2	10/155,918	Transmittal, Fee Sheet <i>in duplicate</i> , Preliminary Amendment	KYB	\$180
CNVG-004US1DIV	09/721,158	PTOL-85B <i>in duplicate</i> , Formal Drawing Transmittal, (70) Sheets, Amendment 1.312	CML	\$665
AGYT-022	10/795,148	Transmittal, Fee Sheet <i>in duplicate</i> , Supplemental ADS, Copy of Notice to File Missing Parts, Executed Declaration, Paper Copy of Seqlist, Seqlist Certification, (1) CD w/Seqlist in CRF	PJS	\$65
CRMD-007	10/792,684	Transmittal, Fee Sheet <i>in duplicate</i> , Copy of Notice to File Missing, Parts, Supplemental ADS, Executed Declaration, Formal Drawing Transmittal, (13) Sheets of Figures	CML	\$567
LIFE-018DIV	10/861,275	IDS, SB08A, Copies of SB08A from Parent, (5) cited References	CML	
UCAL-161DIV	09/922,483	Transmittal, Amendment After Final Rejection, Executed Declaration of R. Stein (Exhibits 1-2)	PAB	
LIFE-094	09/264,786	Transmittal, Fee Sheet <i>in duplicate</i> , PTOL-85B, Notification of Change of Entity Status, (7) Sheets of Figures, IDS, SB08A, (1) Cited Reference	CML	\$1,510